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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,196	03/23/2000	ROGER JOHN DALY	1871-129	8868

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EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,196	DALY ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7,19-22,24-29 and 31-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7,19-22,24-29 and 31-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/25/5*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-50

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 25, 2005 has been entered.

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

3. Claim 22 has been amended as requested in the amendment filed on July 25, 2005. Following the amendment, claims 5-7, 19-22, 24-29 and 31-41 are pending in the instant application.

Claims 5-7, 19-22, 24-29 and 31-41 are under examination in the instant office action.

4. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

6. Applicant's arguments filed on July 25, 2005 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

7. Claims 5-7, 19-22, 24-29 and 31-41 stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for reasons of record in appropriate sections of previous office actions of record.

Applicant traverses the rejection on the premises that "the claimed invention has two utilities:

1) The claimed polynucleotides are useful in distinguishing cancer cells from normal cells, e.g., breast cancer cells

2) The claimed polynucleotides are useful for distinguishing cancer cells from normal cells since they encode a polypeptide that binds to Grb7 and Grb14, each of which are known to be differentially expressed in cancer cells relative to normal cells" (bottom at page 6 of the Response). Applicant further points out that the second asserted utility, as to the ability of the 2.2412 polypeptide to bind and consequently detect Grb7 and Grb14, which are asserted to be differentially expressed in cancer as compared to normal cells, was not properly addressed by the Examiner in the previous office action (top at page 7). At pages 7-9 of the Response, Applicant reviews publications available before the filing of the instant application, which allegedly support the asserted utility of 2.2412 polypeptide encoded by the claimed polynucleotides, and argues that the instant claims are fully supported by a disclosure of utility sufficient to satisfy 35 U.S.C. 101. Applicant's arguments have been fully considered but are not persuasive for reasons set forth below.

Briefly, the instant specification, as filed, discloses a polypeptide of SEQ ID NO: 2, designated 2.2412 polypeptide, which is encoded by a polynucleotide of SEQ ID NO: 1. The

instant 2.2412 polypeptide was isolated based on its ability to bind to Grb14 protein within yeast two hybrid screen system (see pages 6-10 of the specification). It was further hypothesized that because Grb14 is related to Grb 7 and Grb 7 is differentially expressed in certain human cancers, the protein that binds to Grb14 could be useful as tumor marker (middle at page5, for example). The pattern of tissue distribution of 2.2412 protein is such that it is expressed "in all tissues examined with the exception of the kidney" (middle at page 10).

First, it is important to point out that the first asserted utility to use the claimed 2.2412 encoding polynucleotides as a marker for cancer appears to be lacking any factual evidence within the instant disclosure. Contrary to Applicant's statement, there is no information presented at the time of filing regarding "differential expression of the claimed 2.2412-encoding polynucleotide itself" (top at page 7 of the Response). Absent a disclosure of altered levels or forms of a polynucleotide encoding 2.2412 polypeptide in diseased tissue as compared with the corresponding healthy tissue, the claimed polynucleotide is not "useful in distinguishing cancer cells from normal cells", including breast cancer cells (bottom at page 6). Significant further research would have to be conducted to identify diseases (cancer) states, which correlate with altered levels or forms of the claimed polynucleotides.

Determination of which types of cancer are involved and how the claimed polynucleotides are altered during the course of disorder clearly requires significant further research. With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility

in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in specific disclosed levels in diseased tissue compared to normal tissue (i.e. overexpression). However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information regarding general tissue expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. In the instant case, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

With regard to the second asserted utility, Applicant argues that the claimed polynucleotides have patentable utility because they encode proteins, which bind to Grb7 and Grb14 polypeptides, which are allegedly differentially expressed in cancerous cells relative to normal cells. However, the prior art of record as presented in the articles cited by Applicant fails to support Applicant's statement that "Grb7 and Grb14 are recognized as markers for cancer at the time of filing of the present application" (bottom at page 7). Specifically, article by Daly

(Cell Signal, 1998, 10, 613-618) presents data regarding tissue distribution of Grb7 and Grb14, which are disclosed as being highly expressed in wide variety of different normal tissues (p.614, second column) and a reference to a publication by Stein et al. (EMBO, 1994, 13, 6, 1331-40) regarding correlation between overexpression of Grb7 and ErbB2 in breast cancer cell lines as well as primary breast cancer specimens (p.615, first column). However, it is clear from the article of Stein et al. that research data of Grb7 being associated with breast cancer was inconclusive at the time of publication: "[w]hether GRB-7 expression, like HER-2, has prognostic significance in patients with primary breast cancer remains to be seen. Although our data indicate a highly significant correlation between overexpression of HER-2 and overexpression of GRB-7 in patient samples, the relationship is imperfect; 24 out of the 34 specimens overexpression HER-2 also overexpressed GRB-7 but 10 do not".

Further, articles of Kishi et al. and Tanaka et al. relate to coexpression and co-amplification of Grb7 in gastric and esophageal cancers, respectively. The instant specification, as filed, lacks any reference to an assertion of a specific utility of 2.2412 encoding polynucleotides in these types of cancer. Applicant is reminded that the patent law requires that the specific and substantial credible utility of the claimed invention must be fully disclosed at the time of filing, which precludes any subsequent recitation of asserted utility of the claimed invention.

Also, regarding the data pertained to overexpression of Grb7 in certain cancer calls lines (Applicant's Response at page 8), it is well settled in the art of cell biology that cancer cell lines differ in a number of respects from the cancer cells from which they have derived. Fundamental aspects of these differences include differential expression of proteins, cell-cycle time and

responsiveness to cytotoxic drugs. As discussed in the article by Baguley et al. (Baguley et al., 2004, European J. Cancer, Vol. 40, pp. 794-801), "a potential weakness of [human tumour] cell lines is that they may have lost important properties originally possessed *in vivo*, including potential targets for therapy" (see abstract).

One skilled in the art appreciates that cancer cell lines derive from primary cancer cells through a process of immortalization, which results in a significant alteration in the level and type of proteins expressed by that cell. Whereas it is well known that the transformation of a "normal" cell into a cancer cell can result from an alteration of a single gene, the process of immortalization appears to be much more complex and has a more profound effect on the protein expression profile. Also, the differences between "normal", cancer cells and cancer cell lines are often assumed to reflect features of normal versus malignant biology, but instead are due to different culture conditions. A "normal" cell *in vivo* grows in an environment that is substantially different from the *in vitro* environment of the cell line (artificial culture media, monolayer cultures versus three-dimensional *in vivo* conditions etc.). One of ordinary skill would reasonably expect that changes in the environment in which a cell grown would result in a substantial alteration in the level and type of proteins expressed by that cell.

Furthermore, according to the information available in the art, the rate of cell proliferation of primary cancer cells is different from the corresponding cancer cell line (Baguley et al., p.795, section 2). Finally, cancer cell lines appear to be less sensitive to cytotoxic drugs, including critical anticancer inhibitors of EGFR tyrosine kinase, as compared to primary cancer cultures (page 798, section 4). Therefore, one skilled in the art of cell biology would reasonably conclude that the observed overexpression of Grb14 protein in a prostate or breast cancer cell

line cannot be unequivocally indicative of Grb14 being a marker for these types of cancer (see Applicant's reasoning regarding publication of Daly et al, 1996, J. Biol. Chem., 271, 12502-10).

At pages 8-9 of the Response, Applicant argues that 2.2412 polypeptide specifically binds to Grb7 and/or Grb14 polypeptides and, thus, can be used as a marker for breast cancer in which Grb7 is allegedly differentially expressed. Regarding the merit of the argument, even if to assume that the instant 2.2412 polypeptide specifically binds to Grb7 to the exclusion of all the other proteins and therefore would be useful to specifically recognize Grb7, the issue at hand remains tat there appears to be no support in the instant specification or prior art of record that would indicate that Grb7 proteins are diagnostic of breast cancer.

Applicant's asserted utility for the polynucleotide encoding the polypeptide 2.2412 of SEQ ID NO: 2, particularly in view of a lack of knowledge as to the biological function of the polypeptide of SEQ ID NO: 2, the type of cancer which can be diagnosed and how much of 2.2412 polypeptide/polynucleotide is indicative of disease, constitutes a utility that requires further research to identify or reasonably confirm a "real world" context of use. See *Brenner v. Manson*, 148 USPQ at 696. While an assay that detects the presence of an agent that has a stated correlation to a predisposition or presence of a specific disease condition would be considered a "substantial utility" in the context of identifying potential candidates for preventive measures, in the instant case the claimed polynucleotides are suitable only for future research.

Thus, for reasons set forth and also reasons of record in the previous communications of record, the claimed polynucleotides do not have a real-world use and do not meet the utility requirements under 35 U.S.C. 101.

Claim Rejections - 35 USC § 112

8. Claims 5-7, 19-22, 24-29 and 31-41 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.

Primary Examiner
Art Unit 1649

September 7, 2005